Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

ORIGINAL

In re	)	
	)	
Proposed Rule on	)	
Dietary Supplement Products	)	Docket No 95N-0304
Containing Ephedrine Alkaloids	)	
	)	
	)	
	)	

JOINT COMMENTS OF DURK PEARSON AND SANDY SHAW, BIOGENICS, INC, WEIDER NUTRITION INTERNATIONAL, INC , and JULIAN M WHITAKER, M D.

Jonathan W Emord
Andrea G Ferrenz
Emord & Associates, P C
1050 17th Street, N W
Suite 600
Washington, D C
(202) 466-6937

Dated December 2, 1997

95N-0304

C 3386

TABLE OF CONTENTS

Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

In re.	)	
	)	
Proposed Rule on	)	
Dietary Supplement Products	)	**Docket No 95N-0304**
Containing Ephedrine Alkaloids	)	
	)	
	)	
	)	

JOINT COMMENTS OF
DURK PEARSON AND SANDY SHAW;
BIOGENICS, INC,
WEIDER NUTRITION INTERNATIONAL, INC , and
JULIAN M WHITAKER, M D

The Food and Drug Administration (FDA) has invited public comment on its Proposed Rule in the above-referenced proceeding ("Proposed Rule") Durk Pearson and Sandy Shaw, Biogenics Inc , Weider Nutrition International, Inc , and Julian M Whitaker, M D ("Joint Commenters") hereby respond to that invitation by submitting comments for the FDA's consideration

BACKGROUND OF THE COMMENTERS

Durk Pearson and Sandy Shaw Pearson and Shaw are scientists, maintaining residences in Nevada and California They design dietary supplement formulations and license them to small manufacturing and retailing companies They are authors of four books on aging and age-related diseases, including the #1, million plus copy best seller ***Life Extension. A Practical Scientific Approach*** (1982) They have also published three other health books, two of which were best sellers ***The Life Extension Companion*** (1984), ***The Life Extension Weight Loss Program*** (1986), and ***Freedom of Informed Choice—FDA Versus Nutrient Supplements*** (1993) Pearson and Shaw license dietary supplements that contain ephedrine alkaloids Adoption of the Proposed Rule would have an adverse economic impact upon Pearson and Shaw In addition, Pearson and Shaw wish to communicate the statements set forth on page 24 as additional information on their products The prohibitions limiting labeling to recommending conditions of use at less than 8 mg per dose or a total daily intake of 24 mg and for no more than 7 days would appear to ban the representations they wish to make on the label, thereby violating their First Amendment rights Pearson and Shaw ask the agency to modify its Proposed Rule to avoid the resulting suppression of that speech they wish to communicate

Biogenics Inc. Biogenics, Inc is a Utah corporation that sells a wide range of dietary supplements nationally, including supplements that contain ephedrine alkaloids Adoption of the Proposed Rule would have an adverse economic impact upon Biogenics, Inc, by mandating costly changes in their existing formulas, labels and labeling

Weider Nutrition International, Inc. Weider Nutrition International, Inc ("Weider") is a Utah corporation that is the largest supplier of health, fitness and wellness

products in the world Weider manufactures and markets products in the sports nutrition, bottled drink energy and endurance, diet, natural vitamin and nutritionally-based snack bar categories, including supplements that contain ephedrine alkaloids Weider has been a health, fitness and sports nutrition leader for nearly fifty years since its founding in 1939 Adoption of the Proposed Rule would have an adverse economic impact on Weider forcing the company to change its labels and labeling and its product formulas in costly ways

Julian M Whitaker, M.D Julian M Whitaker, M D is a physician licensed to practice medicine in the states of California and Washington He graduated from Dartmouth College in 1966 with a B S degree and from Emory University in 1970 with an M D degree He received additional training in surgery as a resident at the University of California Medical School From 1975 to 1976 he worked as a physician at the Pritikin Institute in California. Since that time he has been the Clinical Director of the Whitaker Wellness Institute in Newport Beach, California He is the author of five books ***Reversing Heart Disease*** (1985), ***Reversing Diabetes*** (1987), ***Reversing Health Risk*** (1989), ***Natural Healing*** (1994), and ***What Your Doctor Won't Tell You About Bypass*** (1995) Since August of 1991 he has been the editor of Health & Healing, currently the largest single editor health newsletter in the United States In 1996, Health & Healing had over 750,000 subscribers Dr Whitaker has formulated certain dietary supplements that contain ephedrine alkaloids for sale through Healthy Directions, Inc , a Maryland corporation that holds licenses for the sale of his dietary supplement formulas Adoption of the Proposed Rule would have an adverse economic impact upon Dr Whitaker

I INTRODUCTION

The Proposed Rule is arbitrary and capricious and contrary to law in violation of Section 706 of the Administrative Procedure Act (APA), 5 U S C §706[1], and Sections 342 and 343 of the Food, Drug and Cosmetic Act (FDCA), 21 U S C §§ 342, 343[2]

Because the agency has not based its conclusions on scientifically investigated and

---

[1] To the extent necessary to decision and when presented, the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provision, and determine the meaning or applicability of the terms of an agency action The reviewing court shall –

(2) hold unlawful and set aside agency action, findings, and conclusions found to be-

(A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law,

5 U.S C § 706 (1997)

[2] A food shall be deemed to be adulterated-

(a) Poisonous, insanitary, etc , ingredients

(1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health, but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health

(f) Dietary supplement or ingredient: safety

(1) If it is a dietary supplement or contains a dietary ingredient that-

(A) presents a significant or unreasonable risk of illness or injury under-

(i) conditions of use recommended or suggested in labeling, or

(ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use,

21 U.S C § 342 (1996)

A Food shall be deemed to be misbranded-

(a) False or misleading label

If (1) its labeling is false or misleading in any particular, or (2) in the case of a food to which section 350 of this title applies, its advertising is false or misleading in a material respect or its labeling is in violation of section 350(b)(2) of this title

21 U S C § 3434 (1996)

Definitions, generally

(n) If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, work, design, device or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual

analyzed adverse incidence reports, and has not buttressed its assumptions of causality with scientific evidence, its Proposed Rule suffers from fundamental flaws The lack of scientifically valid evidence to support the Proposed Rule renders it arbitrary and capricious Moreover, the agency has failed to prove by a preponderance of the evidence that dietary supplements containing ephedrine alkaloids are adulterated and mislabeled by current conditions of use and labeling

II SUMMARY OF THE PROPOSED RULE

The FDA proposes limits on the use of ephedrine alkaloids in dietary supplements [3] The Proposed Rule specifies a maximum dosage of less than 8 mg of ephedrine alkaloids per serving and requires conditions of use not to equal or exceed 8 mg or more in a 6 hour period (or a total daily intake of 24 mg or more) Under the Proposed Rule, product labeling must include a seven day limit on use, a warning of the consequences of overdose when short-term effects are stated on the label, and another extensive warning statement about the hazards of pre-existing conditions and the use of the product with certain medications Additionally, under the rule, dietary supplements containing ephedrine alkaloids cannot be labeled as having long-term effects such as weight loss

The FDA bases the Proposed Rule on more than 800 Adverse Event Reports (AERs) that it received concerning dietary supplements believed to contain ephedrine alkaloids The AERs do not corroborate the agency's conclusions, however, because the reports are incomplete and unverified The AERs are unscientific, lacking important

---

21 U S C § 321 (1996)

information necessary to determine the cause of the adverse events Many of the AERs are records of consumer abuse of dietary supplements containing ephedrine alkaloids and should not be used in assessing the safety of the products when used as directed Finally, medical examinations and laboratory testing are required to render conclusive diagnoses and to determine causation The FDA has not performed those exams and that testing and, thus, lacks a reliable, scientific basis for its Proposed Rule

III ARGUMENT

A SCIENTIFIC FLAWS

The FDA does not rely on scientifically valid empirical data to support the Proposed Rule The AERs are not scientific They are supposed to be used as a starting point for further investigation Additionally, the causal relationship presumed by the FDA between the symptoms reported in the AERs and the consumption of dietary supplements containing ephedrine alkaloids has not been proven

1. The AERs Are Unscientific

The FDA relies on unverified allegations of harm (its Adverse Event Reports) as the principal basis for its Proposed Rules The evidence fails to prove scientifically that ephedrine alkaloids – as opposed to other substances consumed by the complainants, other medical conditions suffered by the complainants or misuse/abuse of ephedrine-containing products – are the causal agents responsible for the alleged harms

AERs are records of calls made by consumers and some medical professionals to the FDA's reporting hotlines The agency does not verify the information contained in

[3] The FDA cites the following sections of the FDCA as their authority for the Proposed Rule 21 U.S.C. § 321(n), 342(a)(1), 342(f)(1)(A), 343(a)(1), and 371(a) 62 Fed Reg 30678, 30693 and 30699

the calls and reports The agency has no assurance of the accuracy or completeness of the information imparted to it The AERs are not scientific surveys of a population and, therefore, do not provide statistical proof of significance in the overall population

The AERs vary in nature and quality In many cases crucial facts are not included in the reports, such as the name of the product used by the consumer, the dosage actually taken by the consumer, the duration and frequency of use of the product, the patient's prior clinical history, the patient's concurrent use of other drugs or stimulants, and the patient's diet before and after consuming the product Callers did not state whether they had any pre-existing conditions or whether the products generally were taken in conjunction with other dietary supplements, foods, or drugs The foregoing facts are indispensable to determining whether there is a causal nexus between the use of ephedrine alkaloids and any reaction Other factors may be responsible for the reported reactions because they have not been ruled out using a scientifically valid means of screening

Participants at the August 1996 "Food Advisory Committee on Food Products Containing a Source of Ephedrine Alkaloids" (August FAC) raised the issue of AER inadequacies on numerous occasions [4] At the end of the August meeting a number of the participants believed it inappropriate to draw any conclusions based on the data in the AERs Dr George Ricaurte, a consultant to the August FAC, stated, "[t]here is uncertainty as far as I'm concerned on the available data with regard to the ephedrine alkaloids themselves to, with any certainty, say there is a safe level "[5] Dr E Wayne Askew, a member of the August FAC, stated that he was impressed by the number of

---

(1997)

[4] See, August FAC Transcript.

people using dietary supplements containing ephedrine alkaloids without having adverse reactions He based his conclusions on that fact rather than on "the adverse incidence reports which are very difficult to deal with because of the nature of the reports "[6]

Commenters on the Proposed Rule have noted the inadequacies of the AER's [7] Dr Leon S Malmud stated that "many of the reports lack details regarding the temporal relationship between the ingestion of a dietary supplement containing an ephedrine alkaloid and the onset of symptoms "[8] Dr Alvan R Feinstein examined the AERs and found that

> the ingested product is not specifically identified The exact quantity consumed, the duration, and the time of most recent usage is often omitted No mention is made of any additional pertinent medications or dietary supplements The user's previous health status and co-morbidity are not always stipulated Some of the alleged consequences, such as 'patchy myocardial necrosis' and 'serous otitis media' are not attributable to ephedrine Accordingly, the reports are difficult to evaluate, [and cannot be relied upon to support a scientifically valid conclusion that ingestion of ephedrine alkaloids caused the subsequent events] [9]

2 Many of the AERs Record Substance or Supplement Abuse

Many of the reported cases are from abuse of dietary supplements containing ephedrine alkaloids (whether the consumer has admitted the abuse or not) [10] Abuse and misuse are significant issues for any food or drug A consumer may believe that he or she has taken the dietary supplement as directed but in fact has misread or misunderstood the labeling, resulting in symptoms of overdose A consumer may ignore recommended

---

[5] August FAC Transcript, Volume II, at p 221
[6] *Id* at 234
[7] See C2253 containing the comments of six independent scientists and doctors of medicine remarking on the problems with the AER system, and C2092 by Durk Pearson and Sandy Shaw This comment incorporates by reference C2092 by Durk Pearson and Sandy Shaw
[8] Professor of Medicine, Senior Vice President for the Health Sciences Center of Temple University, in comment C1864
[9] Comment C2253 Dr Feinstein is a Professor of Medicine and Epidemiology at Yale University School of Medicine

dose information and consume the supplement in excessive amounts For example, there were 2,252 unsolicited calls of poisoning to regional poison centers in 1991 from the misuse and abuse of over-the-counter medicines containing phenylpropanolamine (with and without caffeine) [11] The FDA should have excluded cases of consumer abuse from its safety determination, it did not The AERs are thus, not an accurate reflection of the effects of all ephedrine alkaloid-containing dietary supplements under ordinary conditions of use

3 The FDA Erroneously Presumes that All Sources of Ephedra Have the Same Potency, Rate of Absorption and Effect

The FDA failed to show that ephedrine alkaloids from different sources have a physiologically identical effect The FDA examined the level of ephedrine alkaloids in more than 125 different dietary supplements The FDA found that the source of the ephedrine alkaloids in the dietary supplements varied The sources included those from raw botanicals, those from powdered plants, and those from concentrated extracts [12] The FDA did not determine, however, if the source of the ephedrine alkaloids was a factor in the occurrence of adverse events The FDA makes the counterintuitive assumption, however, without scientific proof, that ephedrine alkaloids from all sources have the same potency, rate of absorption and effect [13]

4. Medical Examinations and Laboratory Tests Are Required to Prove Causation

In many cases where the dosage taken, duration, and frequency were unknown the FDA based its conclusions on the types of symptoms produced by certain product

---

[10] For an analysis of cases of ephedrine alkaloid abuse in the AERs see the Pearson and Shaw comment, C2092

[11] 10 Amer J Emergency Med 452 (1992) cited in C2253

[12] 62 Fed Reg at 30678-30679

concentrations of ephedrine alkaloids, boldly assuming that the consumer ingested the supplement according to the labeling instructions [14] An AER should not replace a medical exam and laboratory test on an individual who claims to be suffering ill effects from taking a dietary supplement The symptoms the FDA categorized as reactions to dietary supplements containing ephedrine alkaloids include "rapid and irregular heart rhythms, increased blood pressure, chest pain, anxiety, nervousness, tremor, hyperactivity and insomnia "[15] Those symptoms are commonplace in over fifty (50) conditions, including ordinary anxiety [16] Examination and testing are required to diagnose properly the actual condition present FDA has not performed that kind of screening As a consequence, the FDA lacks reliable information upon which to base its Proposed Rule Telephone queries are not scientific means to determine causality Presumed causes are frequently false, masking the actual bases for adverse reactions

5 The FDA's Analysis Is Void of Cogent Reasoning

The FDA's analysis of the AERs to determine causation is unscientific The FDA analyzed the AERs by asking five questions 1) whether there were consistent patterns of symptoms associated with the use of dietary supplements containing ephedrine alkaloids, 2) if those patterns of symptoms were consistent with the available scientific evidence on ephedrine alkaloids, 3) if the relationship between the symptoms and the ingestion of the dietary supplement was "temporally correct," 4) if there was other evidence of causality even in the absence of controlled trials, and 5) if there was a biologically plausible

[13] See Pearson and Shaw comment, C2902
[14] Transcript of August Meeting, Volume I, pg 107-110
[15] 62 Fed Reg at 30678-30679
[16] Search of Merck Manual Online (Merck & Co Inc , Sixteenth Edition, 1992)

explanation for the adverse events [17] The FDA's analysis lacks validity because it does not compensate for, or correct, the unreliable and unscientific AERs Instead, the analysis relies upon that flawed data as an empirical foundation for the argument built atop it

Furthermore, the FDA bases its analysis on a presumed "pattern of symptoms" without defining what makes a pattern The possibilities are quite broad in determining what makes a pattern more than ten percent of the AERs displaying the same symptoms, more than half, more than ninety percent, or any number in between Is an AER considered part of a pattern when it displays one of the many symptoms the FDA associates with ephedrine alkaloids? Alternatively, does each symptom form a separate pattern of occurrences? In its search for a pattern, the FDA did not address whether other possible factors or illnesses could cause the symptoms reported Relying on inadequate data and its faulty analysis, the FDA concluded that the "adverse events that are occurring are caused by the ephedrine alkaloids "[18]

Moreover, the FDA did not prove causation (that the ingestion of the dietary supplements containing ephedrine alkaloids caused the symptoms) Although it uses the term "temporally correct,"[19] the agency did not define when a symptom follows in close enough proximity to the ingestion of a dietary supplement containing ephedrine alkaloids to justify making a causal connection between the two events The agency has not proven that symptoms were in fact caused by ingestion of the ephedrine supplements [20] Ephedrine and pseudoephedrine reach peak plasma levels within 1-2 hours and have a

---

[17] 62 Fed Reg at 30683
[18] 62 Fed Reg at 30690
[19] *Id* at 30689-30690
[20] *Id*

half-life (i e they are present at one-half of their peak level) in 2-3 hours if the urine is acidic or a half-life of 7 5 hours for ephedrine and 21 hours for pseudoephedrine if the urine is alkaline [21] Specific testing of blood levels must be available to draw a conclusion as to a causative relationship between ephedrine alkaloids and reported adverse events in light of this important factor No evidence exists to show that this required testing ever took place to verify a single AER

6 The FDA's Proposed Rule Lacks Requisite Statistical Analysis

To determine the relative importance of the AERs, the FDA should have compared the occurrence of each type of adverse event in the population of users of ephedrine dietary supplements to the occurrence of each type of adverse event in the U S population The "Current Estimates From the National Health Interview Survey of 1994," published by the Center for Disease Control (CDC), includes an estimate of 698,000 cases of tachycardia or rapid heart and 5,737,000 cases of high blood pressure in individuals under 45 years of age in the United States [22] Those numbers represent occurrences of some of the very same symptoms that the FDA has associated with the use of dietary supplements containing ephedrine alkaloids [23] The agency has not proven that the over 800 adverse event reports are an unusually high number in excess of that

---

[21] Cetaruk, E W , C K Aaron, "Hazard of Nonprescription Medications," Emergency Medicine Clinics of North America, 12 483 510, 1994 The pH of a subject's urine can widely vary depending on hydration, osmolarity of the blood, diet (including coffee and common fruit juices), carbon dioxide levels, whether they are a smoker, or whether they are taking medication, including common antacids such as baking soda and most popular calcium supplements An analysis that attempts to determine if symptoms are caused by the ingestion of ephedrine alkaloids must be based on these factors The AERs do not contain this crucial information and cannot be the basis for proving that symptoms were caused by dietary supplements containing ephedrine alkaloids

[22] Vital and Health Statistics December 1995, Series 10, No 193 Data based on household interviews of the civilian non-institutionalized population

[23] A statistical comparison of these national figures to the figures associated with dietary supplements containing ephedrine is only valid if the AERs are a reliable source of information

ordinarily occurring in the population due to causes other than ephedrine ingestion Thus, the FDA has failed to prove any statistical significance to the over 800 figure

7 FDA's Analysis Is Flawed Due to Its Lack of a Risk / Benefit Analysis

A conclusion as to the safety of a product requires a risk / benefit analysis The FDA did not perform that analysis, specifically stating it would make no judgments as to the benefits of dietary supplements containing ephedrine alkaloids [24] The omission undermines the scientific validity of the Proposed Rule [25]

The FDA specifically asked members of the August FAC Meeting to determine the safety of dietary supplements containing ephedrine alkaloids without consideration of evidence of the beneficial uses of ephedrine alkaloids The FDA asked participants to base their opinions primarily on the information presented to them at the two day meeting (which was devoid of benefit data), regardless of their prior experience and knowledge of ephedrine alkaloids or of dietary supplements containing ephedrine alkaloids Several participants and commenters emphasized the faulty nature of asking for a safety determination without a risk / benefit analysis [26] Participants explained that almost every food and every drug has some risk of side effects [27] Focusing solely on risks exaggerates

---

[24] "In this document, the agency makes no evaluation or judgment of the effectiveness of the use of ephedrine in the treatment of obesity " 62 Fed Reg at 30688

[25] Pearson and Shaw Comment, C2092 describes extensively the inadequacy of a conclusion as to the safety of a compound without consideration of the benefits derived from that compound

[26] For comparison, the advisory review panel for determining whether a category of over-the-counter drugs are safe and effective must consider the benefit-to-risk ratio of a drug 21 C F R § 330 10 (1996) Although drugs and dietary supplements are under different statutory requirements under the FDCA, the task before the August FAC was like that of an advisory review panel, to determine the safety of dietary supplement products

[27] When discussing such side effects, Commissioner Dr David Kessler instructed participants to only think in terms of significant events MIs (myocardial infarctions), seizures, or death Transcript of August Meeting, Volume II, pg 224 It is apparent, however, from Dr Davidson's analysis of AERs that only seven of the AERs in the significant risk category are probably related to ephedrine alkaloids and they were all at levels above 15 mg/dosage See this comment, section III, A, 9 pgs 15-16 In contrast, when Dr Lori Love, the FDA scientist from the Office of

potential harm and skews the analysis Dr Donald Jasinski, a consultant to the August FAC, said that he knew of literature on the effectiveness of ephedrine alkaloids, but the literature was excluded from consideration [28] He stated that "there is a long history of people using low dosages of stimulants chronically without major consequences "[29] Dr George Ricaurte, another consultant to the FAC, stated that a margin of safety "had to go to infinity" for dietary supplements containing ephedrine alkaloids because a risk / benefit analysis could not be performed when there was no "perceived benefit "[30] The FDA was willing to use "available scientific evidence and known physiologic effects of ephedrine alkaloids" to draw a connection between dietary supplements and adverse events but was unwilling to use the available scientific data on ephedrine alkaloids to draw conclusions concerning the safety and efficacy of dietary supplements containing ephedrine alkaloids independent of the AERs The process is thus biased – without that scientific objectivity requisite to avoiding arbitrary and capricious decision-making

---

Special Nutritionals who presented the FDA's analysis of the AERs to the FAC, was questioned by Dr Kessler at the August FAC meeting on the number of significant adverse events at levels below 20 mg/dose, she could not tell him exactly the number of cases in that range nor the nature of the cases Instead, she summarized one case, for which she stated the FDA didn't have all the information In this case the consumer died from what appeared to be cardiomyopathy The consumer was a long-term user of a product containing 10 mg of ephedrine alkaloids per serving When Dr Kessler asked Dr Love to go through the case for the FAC to have "the best data we [the FDA] have," Dr Love replied that those limited details were all she knew This incident exemplifies the erroneous and very limited nature of the record underlying the Proposed Rule The Proposed Rule is the result of faulty conclusions made by the FDA on incomplete, unsubstantiated information

[28] Transcript of August Meeting, Volume II, pg 211

[29] *Id* Dr Jasinski recommended 12 5 mg of ephedrine alkaloids per dosage for a total of 30 mg per day but said that could be argued up to 40-60 mg per day This is significantly higher than the Proposed Rule's levels of 8 mg per dosage and 24 mg maximum per day of ephedrine alkaloids This disparity could be an indication that Dr Jasinski took the literature showing the benefits of ephedrine alkaloids and their safe use into account while the FDA relied on AERs as the sole basis of their decision

[30] *Id* at 222

8 Ephedrine-Containing Dietary Supplements Are Safer Than Foods in Common Form

Consumers are at risk of suffering adverse reactions when they ingest any food product, either due to food borne pathogens, allergies, or the quantity of food ingested The risk of suffering an adverse reaction from ephedrine supplements is significantly lower than that from many popular foods in common form The Centers for Disease Control and Prevention (CDC) reports that as many as 9,000 U S deaths and 6 5 million to 33 million U S illnesses are food-related [31] As a consequence, ephedrine-containing dietary supplements, when used as directed, are safer than foods in common form Even assuming that the more than 800 adverse events are all attributable to ephedrine-containing dietary supplements, the incidence of reactions to ephedrine does not equal or exceed that associated with foods in common form To the contrary, extant ephedrine containing supplements are already at least four to five times safer than foods in common form [32] Consequently, the FDA acts arbitrarily and capriciously by imposing a disproportionately more stringent set of regulations on ephedrine-containing dietary supplements than on foods in common form

[31] "Food Safety from Farm to Table A National Food Safety Initiative," Report to the President, May 1997 by the FDA, Dept. of Agriculture, EPA, and CDC
http //www cdc gov/ncidod/foodsafe/report.htm

[32] See Pearson and Shaw Comment, C2092 for further discussion of the statistical significance of ephedrine reactions compared to food reactions Pearson and Shaw calculated that the worst case incidence of ephedrine associated deaths would be 7 per million (which assumed that **all** AERS were causally related to ephedrine containing supplements) while the incidence of deaths from foods in common form is 33 per million

9 Evaluation of the AERs Using Reliable Criteria Reveals the Flaws in the FDA's Analysis

The FDA's analysis of the incomplete, unverifiable AERs is an invalid, unscientific method The FDA's conclusions are contrary to the conclusions of other scientists that have evaluated the AERs using accurate criteria A number of commenters did not come to the same conclusions as the FDA on the safety of ephedrine when assessing the AER's scientifically because of the AER's incompleteness [33] Dr Michael Davidson presented his analysis of the AERs at the August FAC Meeting [34] He analyzed 191 of the case reports with clear, defined criteria, and found that there were only infrequent possible associations between ephedrine alkaloid products and severe effects Dr Davidson found only seven serious adverse events probably related to ephedrine alkaloids and all seven involved consumption of ephedrine at more than 15 mg per dose [35] Although Dr Davidson had based his analysis on the AERs, he concluded -- contrary to the FDA -- that, of the 191 AER case reports he analyzed, only "seven serious

---

[33] See Pearson and Shaw Comment, C2092, and A C E R I.S analysis and comment, C2253

[34] Dr Davidson is an Assistant Professor of Medicine at Rush Presbyterian-St. Luke's Medical Center, the Medical Director of the Chicago Center for Clinical Research, and a fellow of the American College of Cardiology

[35] Dr Davidson defined "serious event" as those events that were fatal, life-threatening, a congenital abnormality or that resulted in persistent or substantial disability He divided the 191 case files into five categories unknown, unrelated, remotely related, possibly related, and probably related Significantly, Dr Davidson called 21 case reports unknown because there was not enough information to make a determination 20 were unrelated as another cause of the adverse event was documented 53 were remotely related as another factor was far more likely to have caused the event. 61 AERs were possibly associated with ephedrine because their symptoms were associated with ephedrine containing products, but other factors were equally or more likely to have caused the event. 36 were probably related to ephedrine if the adverse event was likely associated with ephedrine

events were probably related to the ingestion of dietary supplements containing ephedrine alkaloids "[36]

A. LEGAL FLAWS

In light of the failure of the FDA to rely on scientifically valid empirical data and to verify causation, it cannot meet its burden of proof to support the Proposed Rule In addition, the FDA has failed to prove that statements of nutritional support for long-term use of ephedrine alkaloid-containing dietary supplements are misleading Having failed to meet its burden of proof, the FDA cannot adopt the Proposed Rule without violating the APA requirements that agency rules not be arbitrary and capricious and contrary to law The FDA's Proposed Rule also violates the First Amendment to the U S Constitution, the FDA does not have the constitutional authority to impose a prior restraint on truthful, non-misleading labeling that presents scientific data on the safety of ephedrine alkaloids at or above 8 mg per dose and for a consecutive period beyond 7 days [37]

1 Ephedrine Supplements Have Not Been Shown to be Adulterated

The FDA has failed to prove by a preponderance of the evidence that ephedrine-containing supplements are adulterated. The evidence fails to show that the ephedrine-containing supplements contain poisonous or deleterious ingredients that may render them injurious to health when used as directed. The evidence fails to show that the label recommendations or ordinary use of those products creates a significant or unreasonable risk of illness or injury

---

[36] *Id*

[37] See Pearson and Shaw comment C2092 and Plaintiff's arguments in Pearson and Shaw et al v

The Proposed Rule violates the FDCA because the FDA has failed to prove that dietary supplements with ephedrine alkaloids contain any poisonous or deleterious substance that may render them injurious to health when used as directed [38] To prove that a supplement is injurious to health the FDA must show a reasonable possibility of harm due to adulterated or poisonous substances [39] The FDA has failed to show that the ephedrine alkaloids are the causative agents of adverse events The FDA's analysis is based on incomplete, unscientific and uninvestigated evidence as to the nature and circumstances of the dietary supplements ingested

The DSHEA requires the FDA to prove by a preponderance of the evidence that a dietary supplement is adulterated [40] There are four tests for finding a dietary supplement adulterated [41] Under the Proposed Rule, only dietary supplements that present a significant or unreasonable risk of illness or injury under label recommendations or ordinary use are adulterated The adulteration standard is high, requiring proof that illness or injury is likely under conditions of use at levels proscribed in the Proposed Rule The FDA has failed to prove that dietary supplements containing ephedrine alkaloids are

---

[38] The botanical sources of ephedrine alkaloids including, but not limited to, Ma huang, Ephedra, and Chinese Ephedra are not dietary supplements when in an herbal tea and not for a special dietary use or to supplement the diet. 21 U.S.C. § 321 (ff) Therefore, they are subject only to the adulterated foods standard In that case, ephedrine alkaloids are not added substances and therefore the botanical sources are not adulterated as the quantity of ephedrine alkaloids do not ordinarily render the herbs injurious to health As stated in the Pearson Shaw comment, C2092, the herb is safely used extensively in the U.S. and China

[39] U.S. v. 2,116 Boxes of Boned Beef Weighing Approximately 154,121 Pounds 516 F. Supp. 321 (D.C., Kan., 1981), aff'd 725 F.2d 1481, certiorari denied 469 U.S. 825

[40] 21 U.S.C. § 342(f)

[41] A dietary supplement is adulterated if it is a product or contains an ingredient that 1) presents a significant or unreasonable risk of illness or injury under the recommended conditions of use or ordinary conditions of use, 2) is a new dietary ingredient for which there is inadequate information assuring that the new ingredient is not a significant or unreasonable risk of illness or injury, 3) the Secretary declares it to pose an imminent hazard to public health or safety, or 4) is or contains a dietary ingredient that renders it adulterated under the "poisonous, insanitary etc.,

adulterated because they in fact contain poisonous or deleterious added ingredients which may render them injurious to health or because they present a significant or unreasonable risk of illness or injury when used as directed

2 The FDA Has Failed to Prove that Its Less Than 8mg/dose, 24 mg/day Limits Are Scientifically Valid and Supported

The FDA has failed to prove by a preponderance of the evidence that consumption of ephedrine alkaloids in amounts equal to or greater than 8 mg per dose/24mg per day creates a significant or unreasonable risk of illness or injury.

The FDA has erroneously concluded that dietary supplements containing ephedrine alkaloids in amounts equal to or greater than 8 mg per dose/24 mg per day are adulterated As discussed above, the FDA's basis for that conclusion is unscientific Extensive clinical studies have shown that ephedrine is safe when used as directed at amounts well above the limits in the Proposed Rule [42]

The FDA examined clinical studies but drew unwarranted conclusions on the basis of the reported side effects without consideration of the reported benefits As stated above, any food or drug may have side effects and any determination of safety of a product must be accompanied by a risk / benefit analysis When examining the clinical studies, the FDA did not weigh the nature of the side effects against the benefits resulting

---

ingredients" paragraph for adulterated foods under the conditions of use recommended or suggested in the labeling of such dietary supplements 21 U.S.C. § 342(f)(1)(A), (B), (C), and (D)

[42] Astrup, A., Breum, L., Toubro, S., Hein, P., and Quaade, F. The effect and safety of an ephedrine caffeine compound compared to ephedrine, caffeine and placebo in obese subjects. 16 Int. J. Obesity 269-277 (1992) (60 mg ephedrine plus 600 mg caffeine and 60 mg of ephedrine alone) Astrup, A., Toubro, S., Cannon, S., Hein, P., and Madsen, J. Thermogenic synergism between ephedrine and caffeine in healthy volunteers. 40 Metabolism 323-329 (1991) (10 mg, 20 mg, 10 mg ephedrine plus 200 mg of caffeine, and 20 mg ephedrine plus 200 mg of caffeine) Pasquali, R., Baraldi, G., Cesari, M.P. Melchionda, N., Zamboni, M., Stefanini, C., and Raitano, A. A controlled trial using ephedrine in the treatment of obesity. 9 Int. J. Obesity 93-98 (1985) (75mg per day and 150 mg per day) Pasquali, R., Casimirri, F., et al. Effects of chronic administration

from the use of ephedrine alkaloids The FDA acknowledged that the nature of the side effects of the studies on ephedrine were not as severe as those presented in the AERs [43] The FDA erroneously concluded that the absence of severe side effects in the clinical study was due to the fact that "subjects were withdrawn from the study when adverse effects became evident "[44] That was not the case In fact adverse side effects were generally mild and subjects continued to use the formulas In one study cited by the FDA, 180 patients began the trial and 141 completed it, while only 6 withdrew due to adverse drug effects [45] Contrary to the FDA's statement that all subjects with adverse effects withdrew, patients in fact remained in the study and all side effects reached the placebo level after eight weeks [46]

In addition, widespread use of ephedrine in asthma tablets during the 1970's and 1980's provides further evidence of ephedrine supplement safety Dr Robert W Katz, a member of the August FAC meeting, stated that in his clinical experience he saw very few serious side effects when asthmatic children ingested ephedrine [47] Despite cases of ephedrine overdose by drug abusers, ephedrine is recognized by clinicians as safe when used at recommended levels "Many years of clinical experience with the use of ephedrine as a bronchodilator and nasal vasoconstrictor have demonstrated that the drug

---

of ephedrine during very low calorie diets on energy expenditure, protein metabolism and hormone levels in obese patients 82 Clinical Sci 85-92 (1992) (150 mg per day)

[43] 62 Fed Reg at 30688-30689

[44] *Id*

[45] Astrup, A, et al , The effect and safety of an ephedrine caffeine compound compared to ephedrine, caffeine and placebo in obese subjects Supra, note 36 at 271 In the six that withdrew, two were on caffeine alone, one on ephedrine alone, and three on ephedrine with caffeine

[46] *Id* at 275

[47] August Transcript, Volume II, pg 240

is safe when administered in the recommended doses "[48] The recommended single dose for ephedrine is 15 to 30 mg and 60 mg for pseudoephedrine for decongestants and bronchodilators [49]

3 The FDA Has Failed to Prove That Its 7 Day Limit Is Scientifically Valid and Supported

The FDA has failed to prove by a preponderance of the evidence that consumption of ephedrine alkaloids for more than seven consecutive days creates a significant or unreasonable risk of illness or injury

Clinical studies have shown that ephedrine is safe for use for more than seven consecutive days [50] One particular study treated three sets of subjects (one with a placebo, one with 75 mg of ephedrine per day and one with 150 mg of ephedrine per day for three months) [51] Out of the 62 patients that began the study only 10 were excluded due to undesirable side effects, a number had side effects, including those in the placebo group, but stayed in the study [52] The authors reported that the symptoms were "well tolerated and tended to disappear during the third month of therapy "[53] That study clearly shows that consumption of ephedrine does not create a significant or unreasonable risk of

---

[48] Wooten, M et al, Intracerebral Hemorrhage and Vasculitis related to ephedrine abuse 13 Ann Neurology 337-340 (1983) Case study of 20 year old who ingested an unknown quantity of ephedrine believing it to be the amphetamine "speed "

[49] Emergency Medicine Clinics of North America, supra, note 19

[50] Astrup, A , Breum, L., Toubro, S , Hein, P , and Quaade, F The effect and safety of an ephedrine caffeine compound compared to ephedrine, caffeine and placebo in obese subjects 16 Int J Obesity 269-277 (6 months) Pasquali, R , Baraldi, G , Cesari, M P Melchionda, N , Zamboni, M , Stefanini, C , and Raitano, A A controlled trial using ephedrine in the treatment of obesity 9 Int J Obesity 93-98 (1985) (3 months) Pasquali, R , Casimirri, F , et al Effects of chronic administration of ephedrine during very low calorie diets on energy expenditure, protein metabolism and hormone levels in obese patients 82 Clinical Sci 85-92 (1992) (6 weeks)

[51] Pasquali supra at 94

[52] *Id* at 96

[53] *Id*

illness or injury Indeed, millions of asthmatics have safely taken ephedrine every day for many years, at far higher doses than the FDA proposal

4 The FDA Has Failed to Prove a Significant or Unreasonable Risk of Illness or Injury

The FDA has failed to prove by a preponderance of the evidence that consumption of ephedrine alkaloids in combination with caffeine creates a significant or unreasonable risk of illness or injury.

Well-designed studies have shown ephedrine used in conjunction with caffeine at dosages of 20 mg of ephedrine plus 200 mg of caffeine per serving three times a day, for a total of 60 mg of ephedrine plus 600 mg of caffeine, results in significant weight loss above placebo groups with transient, minimal side effects when taken for 6 months [54] The number of symptoms reported for ephedrine plus caffeine was substantially the same as the number of symptoms for caffeine alone [55] Additionally, by the eighth week of treatment the number of symptoms for ephedrine plus caffeine was substantially the same as the number for the placebo group [56] Those studies show that ephedrine in combination with caffeine is safe This combination does not cause significant or unreasonable risk of illness or injury

5 The FDA Has Failed to Prove Statements of Nutritional Support for the Long-Term Use of Ephedrine Supplements Are Misleading

---

[54] Astrup, et al The effect and safety of an ephedrine caffeine compound compared to ephedrine, caffeine and placebo in obese subjects, supra note 44 Side effects were limited to dizziness, headache, tremor, depressed mood, euphoria, insomnia, postural hypotension, palpitation, and tachycardia and there were only more reports of symptoms in the ephedrine plus caffeine group than the placebo group at week four Id See also, Dullo, A G & Miller D S The thermogenic properties of ephedrine/methylxanthine mixtures human studies 10 Int. J Obesity 467-481 (1986)

[55] There were 27 incidences of symptoms in the ephedrine plus caffeine group and 22 incidences of symptoms in the caffeine group Id at 273

[56] There were three incidences of symptoms in the ephedrine plus caffeine group and three in the placebo group Id

The FDA lacks a statutory basis for prohibiting or limiting truthful and nonmisleading (scientifically substantiated) statements of nutritional support for long-term use of ephedrine alkaloid-containing dietary supplements

A food is misbranded if its labeling is false or misleading in any particular [57] In determining whether labeling is misleading, the FDA takes into account, 1) representations made or suggested on the label or in labeling by statement, work, design, or device, 2) the extent the labeling fails to reveal material facts in the light of such representations, or 3) the extent the labeling fails to reveal material facts with respect to consequences which may result from the use of the article as prescribed by the labeling or customary conditions of use [58]

To quote the agency, "[c]ausality is most readily demonstrated in well-designed and conducted clinical trials, in which the multiple factors that may influence study results and interpretations can be controlled "[59] There are significant clinical studies showing that ephedrine and ephedrine with caffeine are safe (and effective in studies of thermogenesis and obesity) [60] Although the FDA examined some clinical studies on the use of ephedrine and ephedrine with caffeine, it drew unwarranted conclusions about the data and its significance Additionally, the FDA misread one of the studies, stating that it

---

[57] § 343(a)(1)
[58] § 321 (n)
[59] 62 Fed Reg at 30690
[60] As stated above, any analysis as to whether a substance is safe requires a risk-benefit analysis In this case, average weight loss of subjects taking ephedrine plus caffeine was 3 4 kg greater than the placebo group at the end of 24 weeks Astrup, A , Breum, L , Toubro, S , Hein, P , and Quaade, F The effect and safety of an ephedrine caffeine compound compared to ephedrine, caffeine and placebo in obese subjects 16 Int J Obesity 269-277 (1992) Astrup, A , Toubro, S , Cannon, S , Hein, P , and Madsen, J Thermogenic synergism between ephedrine and caffeine in healthy volunteers 40 Metabolism 323-329 (1991) Pasquali, R , Baraldi, G , Cesari, M P Melchionda, N , Zamboni, M , Stefanini, C , and Raitano, A A controlled trial using ephedrine in the treatment of obesity 9 Int J Obesity 93-98 (1985) Pasquali, R , Casimirri, F , et al Effects of

was an obesity study, when in fact the study focused on the thermogenic effects of ephedrine and caffeine in healthy subjects [61] That study examined the effect of ephedrine on healthy, lean individuals, and revealed ephedrine to be safe at doses customarily consumed [62]

6 Prohibiting Truthful and Non-misleading Statements Violates the First Amendment to the U S Constitution

Pearson and Shaw seek to place on the label of their dietary supplement products containing ephedrine alkaloids the following truthful and non-misleading statements [63]

> (1) The traditional dose size for ephedra herb product contains 20 to 60 mg of total ephedra alkaloids One tablespoon of this [i e , the Pearson and Shaw] products contains 20 milligrams of total ephedrine alkaloids from approximately 1 8 grams of ephedra herb That serving size is not approved by the FDA
>
> (2) The traditional use of ephedrine-containing products often exceeds seven consecutive days

In addition, Pearson and Shaw wish to place an asterisk next to each mandated instruction for consulting a health care provider (21 C F R § 111 100 (f)(2)), for limiting product use to 7 days (21 C F R § 111 100 (c)), and for taking more than the FDA-recommended less than 8 mg serving (21 C F R § 111 100 (f)(1)) The asterisk will correspond to another on the bottom of the label next to which will appear the statement The FDA has mandated this instruction

---

chronic administration of ephedrine during very low calorie diets on energy expenditure, protein metabolism and hormone levels in obese patients 82 Clinical Sci 85-92 (1992)

[61] The FDA stated that "the study population of obese individuals is recognized to be less sensitive to the effects of sympathomimetic agents than the general population Certain of these studies also evidence that there is an increased frequency of adverse effects occurring in lean subjects, secondary to sympathetic stimulation, compared to obese subjects that is unrelated to dose per body weight." 62 Fed Reg at 30688

[62] Astrup, A , Toubro, S , Cannon, S , Hein, P , and Madsen, J Thermogenic synergism between ephedrine and caffeine in healthy volunteers Metabolism 40 323-329 1991

[63] These statements are truthful and non-misleading based on the totality of the scientific evidence

The Proposed Rule, 21 C F R §§111 100 (b) and (c), prohibits the statements Pearson and Shaw wish to make, thereby suppressing Pearson and Shaw's right to communicate truthful and non-misleading commercial speech Such blanket suppression of truthful and non-misleading speech has been found unconstitutional [64] Under apposite Supreme Court precedent the FDA's solution should not be to suppress truthful and non-misleading speech but to engage in counterspeech [65] In this rulemaking, to survive First Amendment scrutiny the FDA must make it clear that it would not suppress the foregoing statements but allow them as counterspeech

7. The Proposed Rule Violates the APA

Under the APA, agency action, including rulemaking, is unlawful if it is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law [66] An agency rule is arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider, if it has entirely failed to consider an important aspect of the problem, if it has offered an explanation for its decision that runs counter to the evidence before the agency, or if the rule it adopts is so implausible that it could not be ascribed to a difference in view or a product of agency analysis [67] For an agency rule to satisfy judicial review, the rule must be such that a court "must be certain that it can find that the agency has considered all the important aspects of the issue and articulated a 'satisfactory

[64] Rubin v Coors Brewing Co 514 U.S 476 (1995), 44 Liquor Mart v Rhode Island 116 U S 1495 (1996), Ibanez v Florida, 512 U S 136 (1994), RAV v City of St. Paul, Minnesota 505 U S 377 (1992), Peel v Attorney Disciplinary Comm , 496 U S 110 (1990), Edenfield v Fane 507 U.S 761 (1993)

[65] Ibanez, supra, note 64, RAV, supra, note 64, Peel, supra, note 64

[66] 5 U.S C § 706 (2)(A) (1997)

[67] Motor Vehicle Manufacturer's Association of the United States, Inc v State Farm Mut Auto Ins Co 463 U.S 29, 43 (1983) See also, New York Council, Assoc Of Civilian Technicians v Federal Labor Relations Auth , 757 F 2d 502 (2d Cir), cert denied, 474 U S 846 (1985)

explanation for its action,' [enabling the court to find a] rational connection between the facts found and the choice made "[68]

As explained, *supra*, the FDA has failed to perform a risk / benefit analysis, necessary to determine the safety of an ephedrine supplement It has also failed to confirm the AERs with medical examinations and laboratory tests necessary to prove causation Moreover, the FDA's explanation for its decision is counter to the evidence before the agency and it fails to distinguish between abuse and use directed by the label The FDA based the Proposed Rule on numerous unwritten assumptions that the AERs are scientifically valid and verified when in fact they are not The FDA did not define two key parameters in its analysis, what is considered a pattern of symptoms and what is considered temporally related In addition, the FDA's evaluation lacks requisite statistical analysis to show the context and significance of the occurrence of the over 800 reported adverse events in the population as a whole

The FDA has not considered all the important aspects of dietary supplements containing ephedrine alkaloids nor differentiated between those that contain ephedra herb alkaloid extracts, and those products (which were not reported in association with significant AERs) that contain ground ephedra herb that releases the alkaloids more slowly [69] It has not articulated a "satisfactory explanation for its action " There is not a rational connection between the evidence relied upon and the Proposed Rule Therefore, the Proposed Rule is arbitrary and capricious

---

[68] Henley v Food and Drug Administration 77 F 3d 616, 620 (2nd Cir , 1996) quoting New York Council, Assoc of Civilian Technicians v Federal Labor Relations Auth 757 F2d 502, 508 (2d Cir), cert denied, 474 U S 846 (1985)

[69] See Pearson and Shaw comment C2092 (where Pearson and Shaw explain why pure ephedrine is not the same as an ephedra herb alkaloid extract, which, in turn, is not the same as ground ephedra herb)

The FDA drew unwarranted conclusions about the scientific studies available on the use of ephedrine alkaloids It ignored studies that show ephedrine is safe when used as directed at amounts far above the 8 mg limit in the proposed rule It ignored studies that show ephedrine is safe when used as directed for consumption in combination with caffeine and for use significantly longer than seven consecutive days The agency ignored studies that reported that ephedrine when used with caffeine promotes weight-loss For those reasons, too, the Proposed Rule is arbitrary and capricious

IV CONCLUSION

The Joint Commenters have shown that the Proposed Rule lacks a scientific foundation in empirically valid data They have shown that the agency has not met its burden of proof in 21 U S C § 343 (f) (the adulteration standard for dietary supplements) to justify the Proposed Rule Moreover, the Joint Commenters have shown that statements of nutritional support for the long-term use of ephedrine supplements are not misleading and that banning such statements is therefore a violation of the First Amendment to the U S Constitution Finally, the Joint Commenters have shown that the Proposed Rule is arbitrary and capricious and contrary to law

Respectfully submitted,

DURK PEARSON and SANDY SHAW,
BIOGENICS, INC ,
WEIDER NUTRITION
INTERNATIONAL, INC , and
DR JULIAN M WHITAKER

By _____
Jonathan W Emord
Andrea G Ferrenz
Their Attorneys

Emord & Associates, P C
1050 Seventeenth St , N W
Suite 600
Washington, DC 20036
(202) 466-6937

Dated December 2, 1997